

# The Clinical Consequences of Stimulant Use: Focus on Intoxication, Washout, and Therapies

JoAn Laes MD

Timothy Wiegand MD

Jeremiah Fairbanks MD

Ian Latham MD

Cole Pueringer MD

Lewis Nelson MD

Emily Brunner MD

Friday April 5, 2024



# Disclosure Information

The Clinical Consequences of Stimulant Use: Focus on Intoxication, Washout, and Therapies

Friday April 5, 2024

JoAn Laes MD

Timothy Wiegand MD

Jeremiah Fairbanks MD

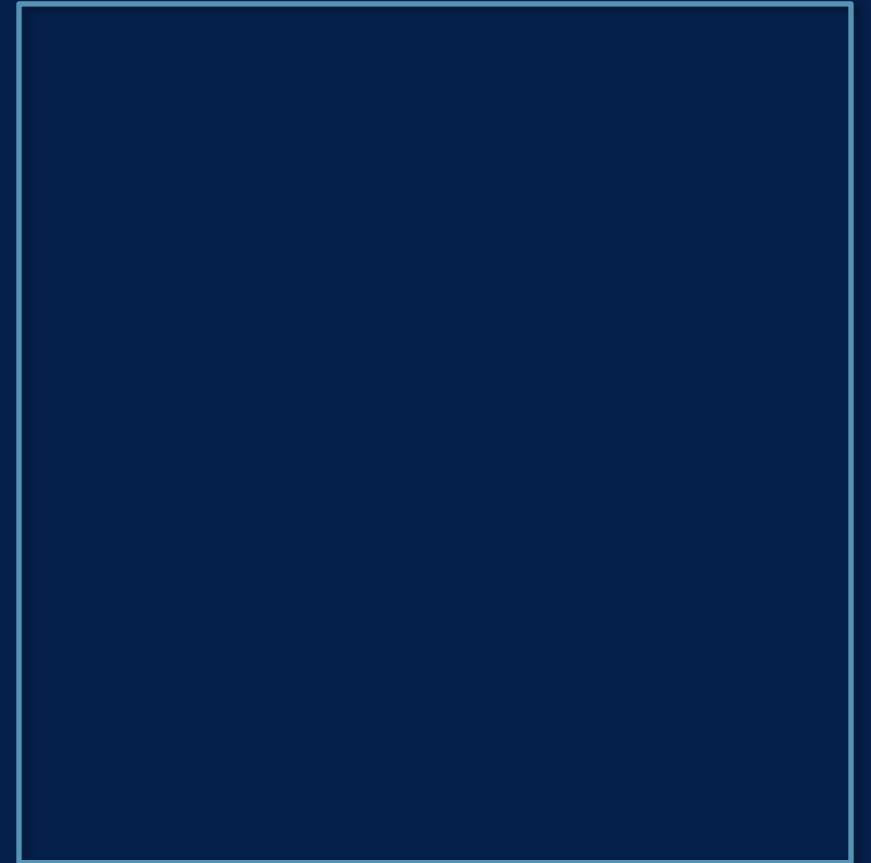
Ian Latham MD

Cole Pueringer MD

Lewis Nelson MD

Emily Brunner MD

◆ No Disclosures

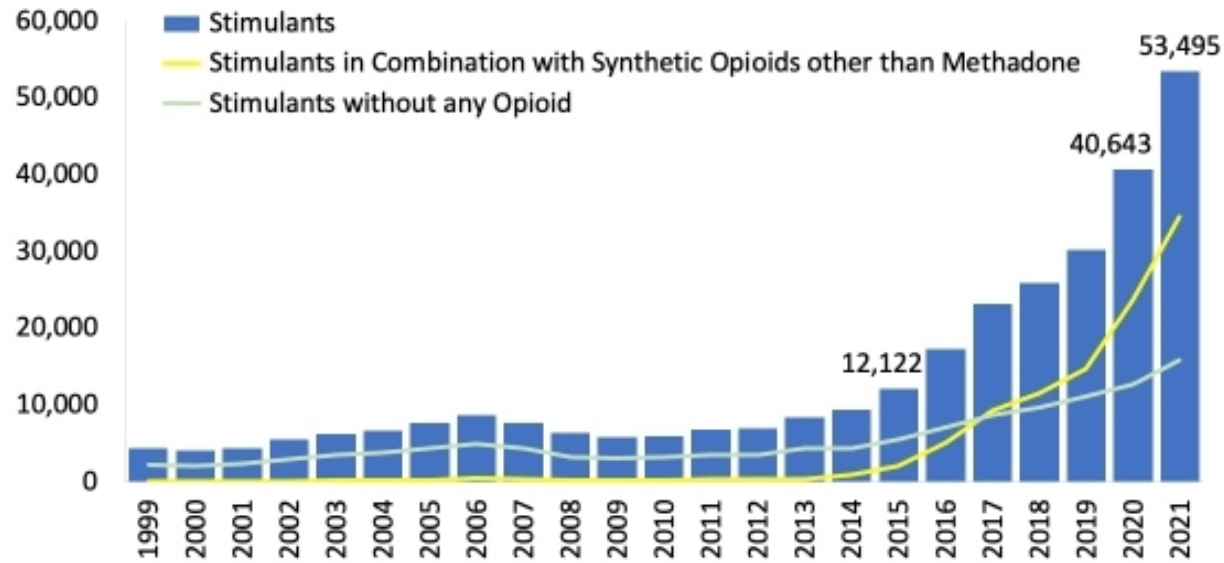


# Learning Objectives

- ◆ Describe the neurobiological effects of various stimulant classes
- ◆ Explain how to assess (including laboratory testing and analysis) and manage stimulant toxicity and wash out syndromes related to stimulant abstinence
- ◆ Highlight the pharmacology and adverse effects of medications used in the treatment of stimulant intoxication and stimulant use disorder

# 4th Wave of Stimulant Mortality

Figure 6. National Overdose Deaths Involving Stimulants (Cocaine and Psychostimulants\*), by Opioid Involvement, Number Among All Ages, 1999-2021



\*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

The ASAM/AAAP  
**CLINICAL PRACTICE GUIDELINE ON THE**

# Management of Stimulant Use Disorder

## The ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder

### **Clinical Guideline Committee (CGC) Members (alpha order):**

Steven Batki, MD; Daniel Ciccarone, MD, MPH; Scott E. Hadland, MD, MPH; Brian Hurley, MD (*Co-Chair*); Kimberly Kabernagel, DO; Frances Levin, MD; James McKay, PhD; Larissa Mooney, MD (*Co-Chair*); Siddarth Puri, MD; Richard Rawson, PhD; Andrew Saxon, MD; Kevin Sevarino, MD, PhD; Kevin Simon, MD; Timothy Wiegand, MD

### **ASAM Team:**

Maureen Boyle, PhD; Amanda Devoto, PhD; Taleen Safarian; Sacha K. Song, MD (medical editing support)

### **AAAP Team:**

Kathryn Cates-Wessel, Michelle Dirst

### **IRETA Team:**

Dawn Lindsay, PhD; Piper Lincoln, MS; Peter Luongo, PhD

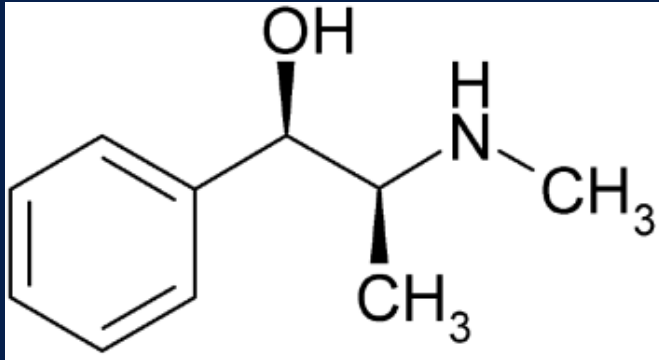
**Funding:** The development of this Guideline was generously funded with contract support from the Centers for Disease Control and Prevention (CDC) and the National Institute on Drug Abuse (NIDA).

**ASAM and AAAP are honored that this clinical practice guideline has been endorsed by:**

The American College of Medical Toxicology  
The American Society for Adolescent Psychiatry  
The American Society of Addiction Nursing

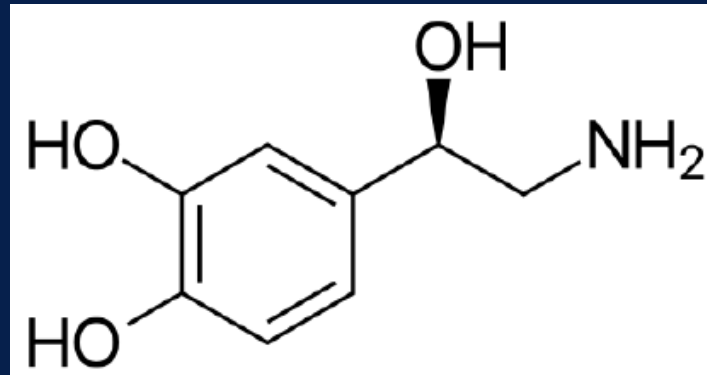


# Building Blocks of the Stimulant Drug Class



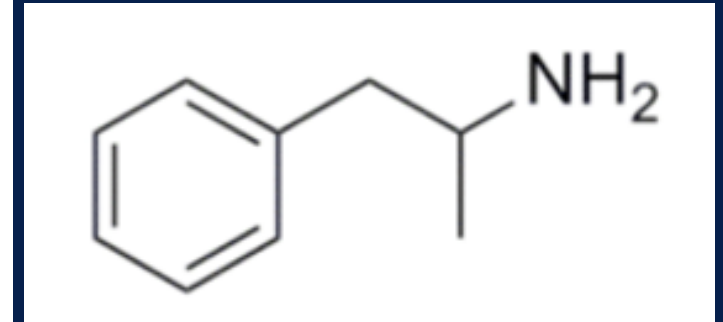
**Ephedrine**

Natural alkaloid derived from the Ephedra Plant



**Norepinephrine**

AKA “Adrenaline” the body’s natural “stress” NT and hormone

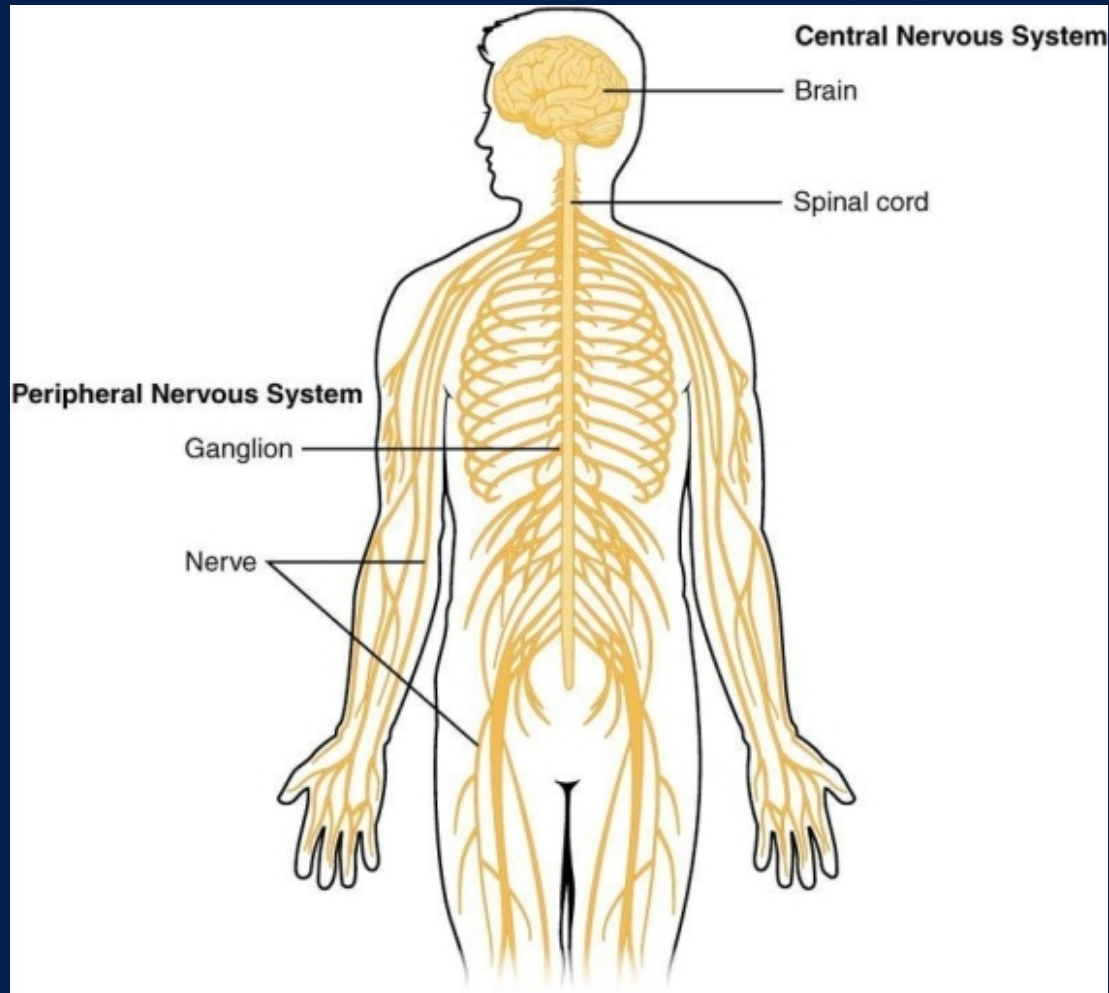


**Amphetamine**

“Prototype” of Stimulant Drug Class

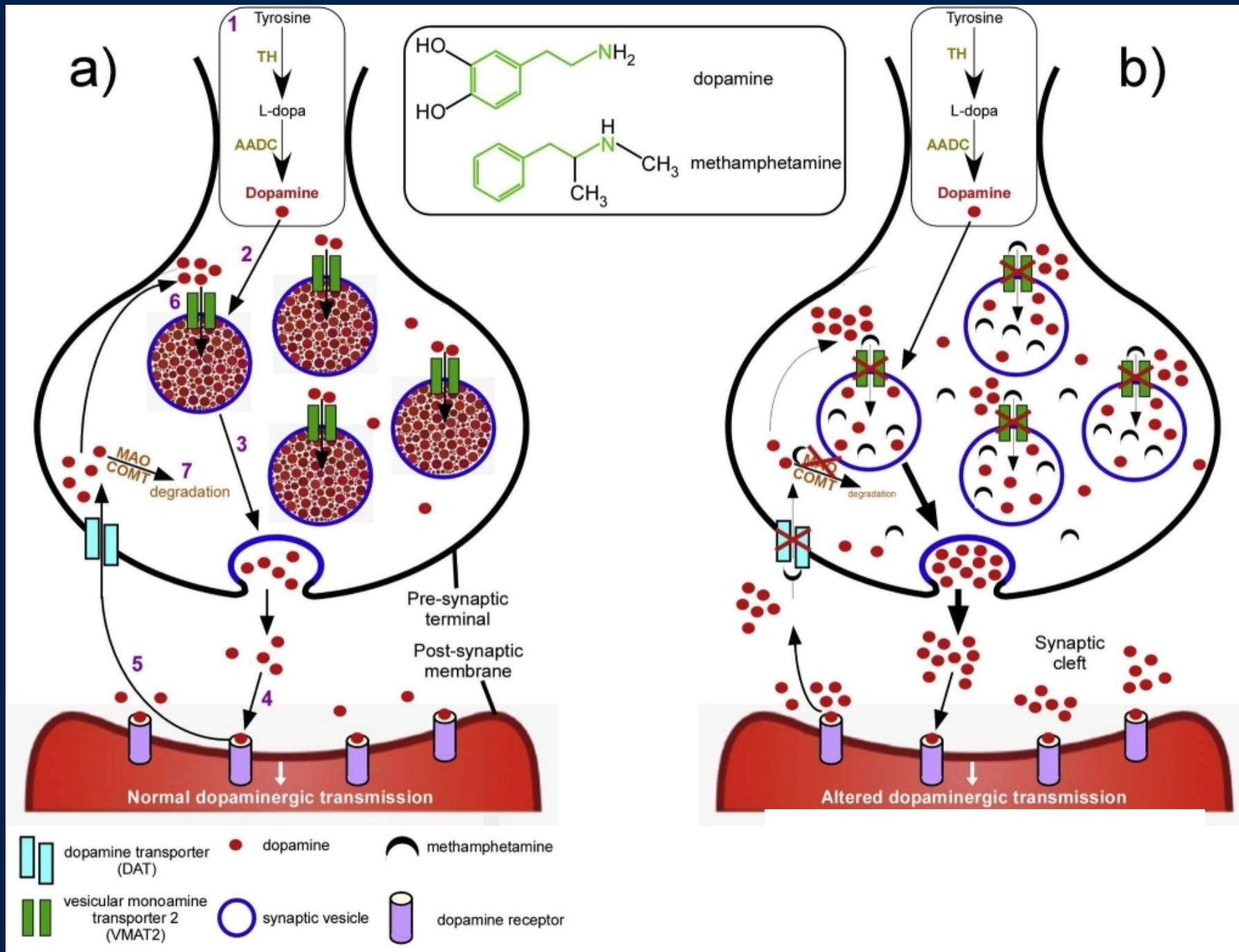


# Stimulant Physiology



- ◆ Broad class of drugs which increase the activity of the central nervous system (CNS) and peripheral nervous system (PNS)







- Emotions
- Sleep
- Mood
- Appetite
- Hallucinations
- Antidiuretic Hormone

Serotonin

Norepinephrine

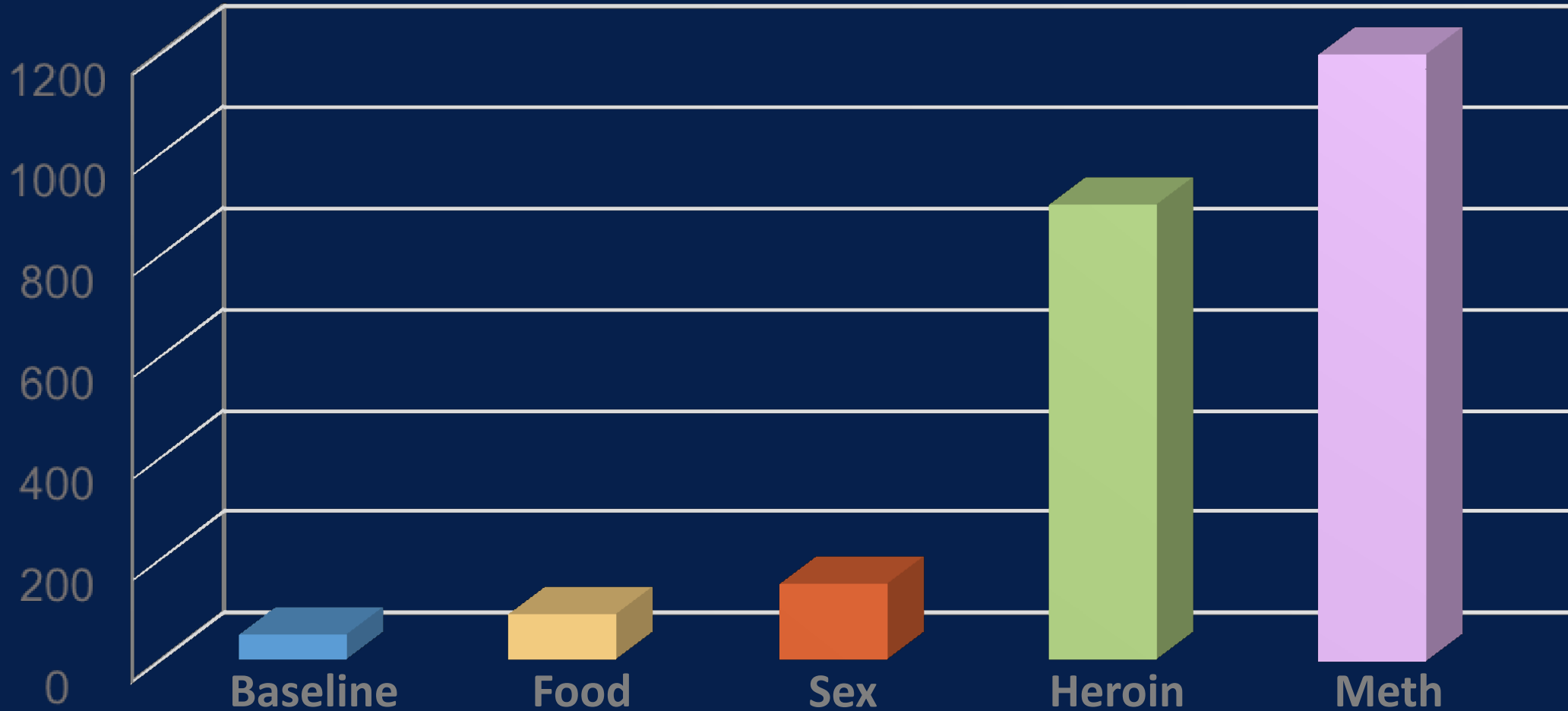
- Alpha receptor
  - Vasoconstriction
  - Hypertension
  - Mydriasis
- Beta receptor
  - Tachycardia
  - Myocardial contractility
  - Peripheral vasodilation
  - Bronchodilation

Alertness,  
arousal,  
stress,  
energy,  
pleasure

Dopamine

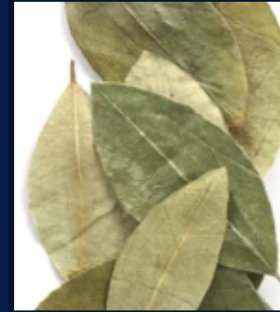
- Motivation
- Reward
- Movement
- Euphoria

# Relative Dopamine Release



# Historical Stimulants

- Ma-Huang (Ephedra) Chinese Traditional herb in 3000 B.C.
- Coca leaf 0 A.D.
- 1860: Isolation of cocaine from coca leaf
- 1887: Synthesis of amphetamine
- 1980: Crack Cocaine (free base of cocaine)



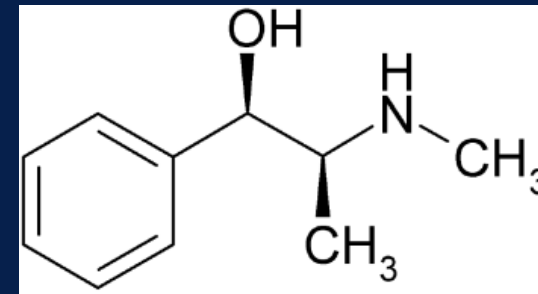
Coca Leaf



Ephedra plant



Ephedra Products



Ephedrine Molecular Structure

# Current Stimulants

## Non-Medical

- Amphetamines
- Cocaine
- Methamphetamine
- Methylenedioxymethamphetamine (Ecstasy/“Molly”)
- Substituted phenethylamines

## Medical

- Amphetamine (Adderall<sup>®</sup>, Bensedrine<sup>®</sup>)
- Dextroamphetamine (Dexedrine<sup>®</sup>)
- Lisdexamfetamine (Vyvanse<sup>®</sup>)
- Methamphetamine (Desoxyn<sup>®</sup>)
- Methylphenidate (Concerta<sup>®</sup>, Ritalin<sup>®</sup>)

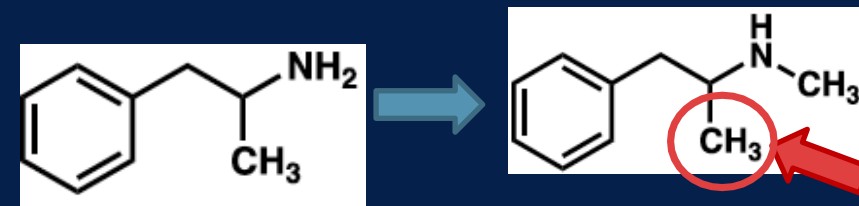
# Methamphetamine (METH)

## Methamphetamine History

- Developed in early 20th century from amphetamine
- Initially used in *nasal decongestants* and *bronchial inhalers*
- Still available by Rx in U.S. (Desoxyn®)

## Meth differs from amphetamine and cocaine

- Greater amounts of drug cross BBB
- Longer duration of effect in the brain
- More potent



Amphetamine

Methamphetamine

Replacement of the hydrogen with a methyl group puts the “meth in “methamphetamine”



Crystal  
methamphetamine

Source: DEA



METH in finished form

Source: DEA



# Methamphetamine Vs. Cocaine

## Cocaine

- Plant-derived
- Euphoric effect lasts 20-30 minutes
- T  $\frac{1}{2}$ : 1 hour
- Mechanism:  
inhibit dopamine reuptake  
(bind DA transporter)
  - Local anesthetic (sodium channel blockade)

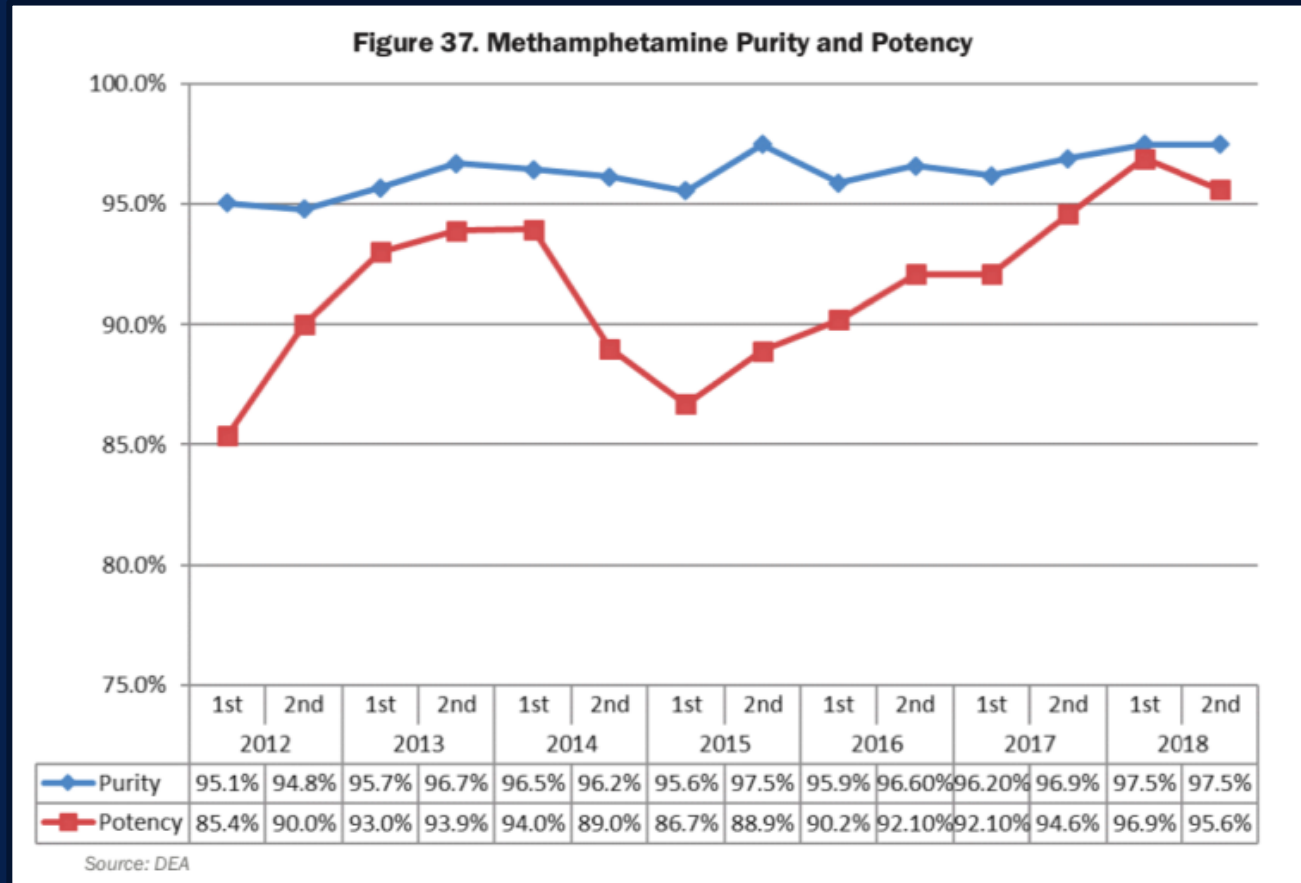
## Methamphetamine

- Synthetic
- Euphoric effects lasts 4-8 hours
- T  $\frac{1}{2}$ : 12 hours
- Mechanism:
  - Release NE, DA, 5-HT
  - Blocks breakdown of monoamines
- Medical use (Rx as Desoxyn)
- ?Greater neurotoxicity



# METH Purity And Potency Are Increasing

## DEA Methamphetamine Profiling Report (2006 – 2018)



Purity

Potency

# Novel Psychoactive Stimulants

Aegis' Synthetic Stimulant Test Menu (as of 11/1/2023)

2-Fluoromethamphetamine**	Butylone*	N-ethyl Heptedrone*
3/4-Fluoromethamphetamine**	Chloro-N,N-DMC*	N-ethyl Hexedrone*
3/4-Methylmethcathinone*	Dimethylone*	N-ethyl Pentedrone*
3,4-DMMA**	Eutylone*	N-propyl Butylone*
4F-3-methyl-alpha-PVP*	MBZP**	NM N-cyclohexyl Methylone*
4-Fluoromethylphenidate**	MDPHP**	N,N-dimethyl Pentylone*
Alpha-D2PV*	Methylenedioxy-PV8*	Pentylone*
Alpha-PiHP*	N-butyl-Hexedrone*	TFMPP**
Alpha-PHP*	N-cyclohexyl Butylone*	
Benzylone*	N-cyclohexyl Methylone*	

\*Denotes synthetic cathinone

\*\*Non-cathinone stimulant

# Synthetic Cathinone Detections



Figure 1. Select Synthetic Cathinone Detections, 2020-2023

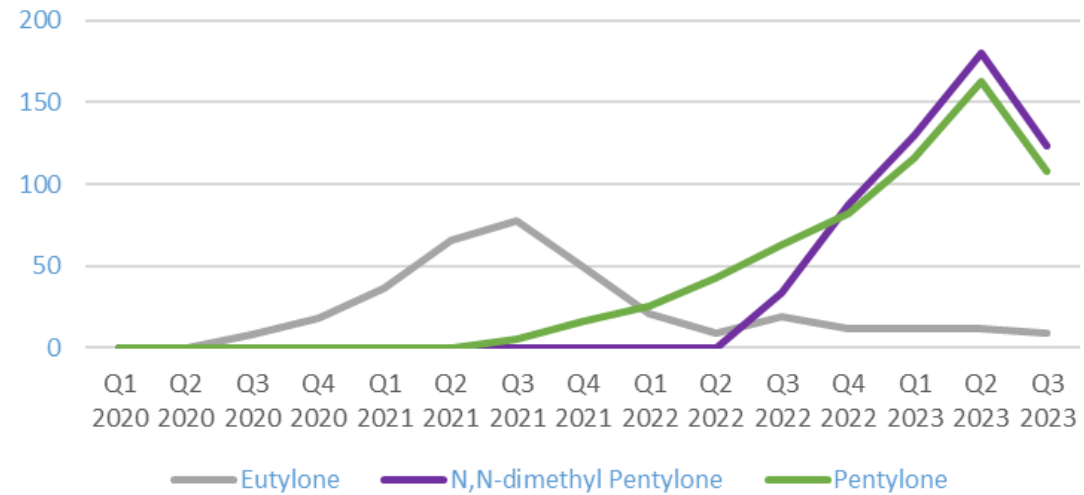
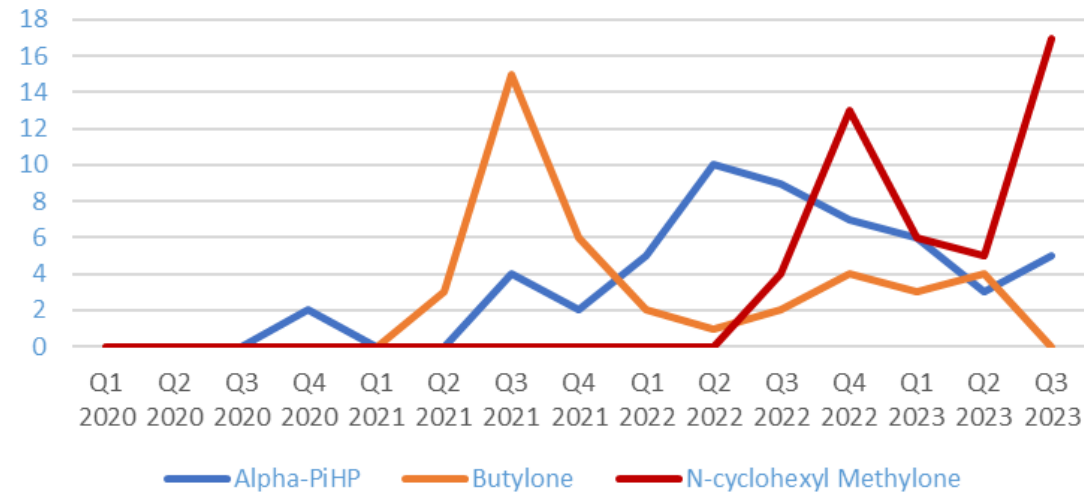
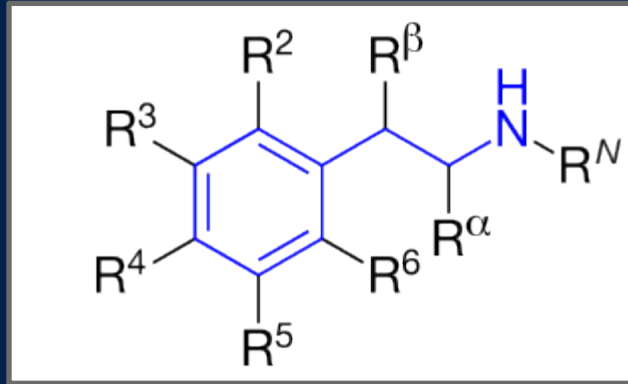


Figure 2. Select Synthetic Cathinone Detections, 2020-2023

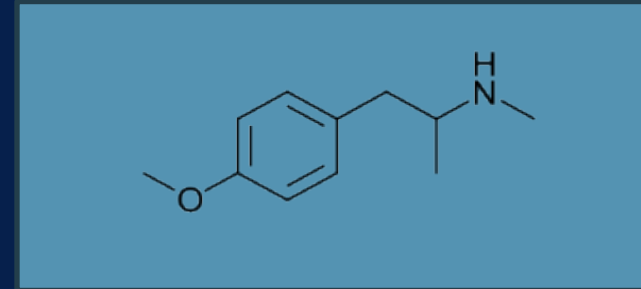


# Substituted Phenethylamines



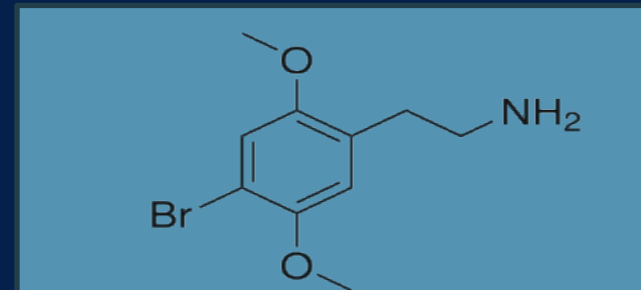
## Para-Methoxyamphetamine (PMA)

Potent hallucinogen, Sympathetic Excess



## 4-Bromo-2,5 methoxyphenethylamine (2CB, MFT)

sensory distortion, hallucination



# Stimulant Adverse Effects



## Psychiatric

Psychosis  
Mood disturbance

- Depression
- Panic

Paranoia



## Cardiovascular

Tachycardia  
Arrhythmias  
Myocardial infarction  
Hypertension  
Stroke  
Cardiomyopathy



## Metabolic

Hyperthermia  
Rhabdomyolysis  
Multisystem Organ  
Failure



## Neurologic

Serotonergic excess  
Seizures  
Choreoathetoid  
movements

Additional causes of agitation and psychosis include (but are not limited to)

- Nutritional deficiencies (eg, Wernicke encephalopathy)
- Neurologic disorders (eg, Parkinson's disease, dementia)
- Brain tumors
- Infections
  - Meningitis, encephalitis, sepsis
- Endocrine dysfunction
- Thyroid toxicity (eg, thyrotoxicosis)
- Hormonal abnormalities (eg, steroid-induced psychosis)
- Autoimmune diseases
- Medication reactions that cause neuropsychiatric symptoms

## Differential Diagnosis



# Psychosis

After cocaine use, psychosis usually resolves after several weeks

- Visual and tactile hallucinations are more common than with a primary psychosis (usually auditory)

Psychosis after methamphetamine use however can be more chronic

- Up to 30% of those using methamphetamines with psychosis report this as persistent after 6 months, and this has been reported in a significant percentage of patients for years after cessation of use



# Management of Psychiatric Effects

Stimulant induced psychosis/mania

- Treat with antipsychotics
  - Consider olanzapine, quetiapine
  - Avoid chlorpromazine, clozapine due to seizure risk
- Gradual taper after symptom remission

In pre-existing psychiatric disorders generally continue medications

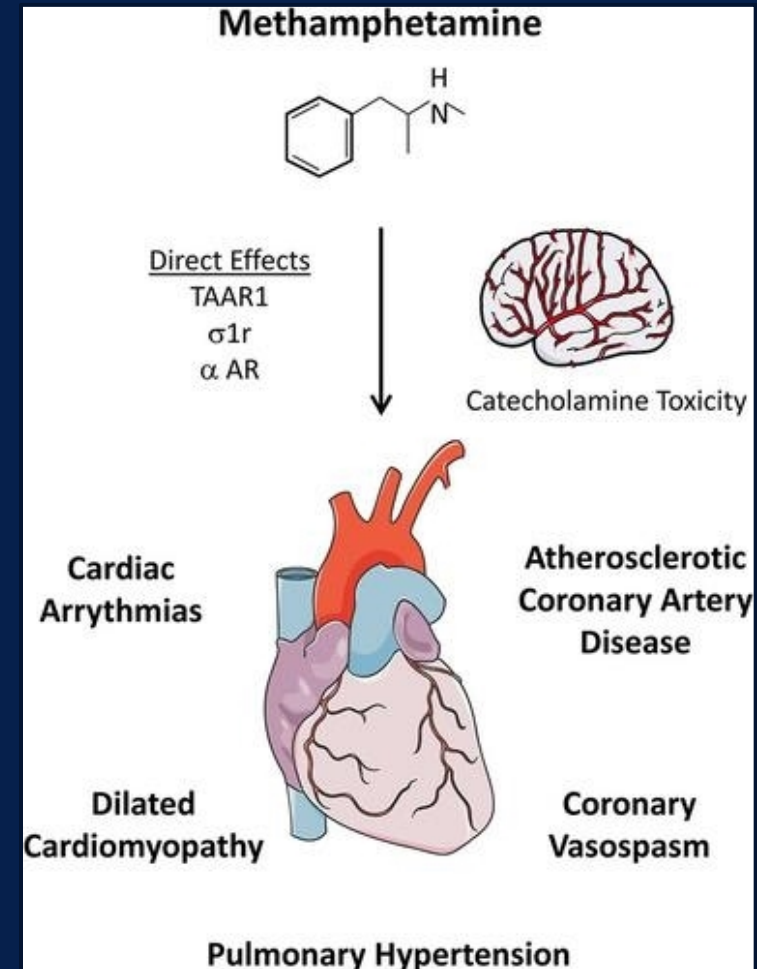
- Note any potential interactions between stimulants and prescribed medications
- Note adherence and effectiveness potentially decreased
- Special attention to ADHD

During stimulant intoxication/catecholamine depletion

- Treat depression, anxiety, insomnia, attention symptoms

# Cardiac Effects of Stimulants

- ◆ **CV disease** occurs through catecholamine toxicity and through direct effects on cardiac and vascular tissue
- ◆ **Pulmonary hypertension**
- ◆ **Myocardial infarction** often results from meth-induced acute coronary vasospasm and enhanced atherosclerotic plaque formation
- ◆ **Remodeling of cardiac tissue** following meth exposure promotes **dilated cardiomyopathy** and may enhance the susceptibility to **cardiac arrhythmias**



# Specific stimulants and PEARLS










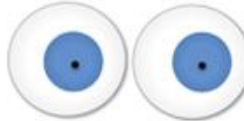




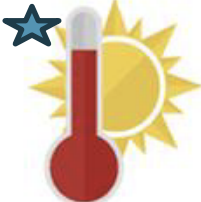









- ◆ Cocaine and cardiovascular toxicity (cocaine chest pain debate)
- ◆ Cocaine and local-anesthetic effects (QRS widening)
- ◆ Cocaine and levamisole
- ◆ Methamphetamine –associated impulsive behavior (traumatic injury, STI prevention/treatment/screening, assault/DV)
- ◆ MDMA and hyperthermia/hyponatremia
- ◆ Bupropion and seizures
- ◆ Cathinone comment ‘aka bath salt’

# Other Factors

- ◆ Adulterant/contamination
  - ◆ Opioids
  - ◆ Alpha agonists










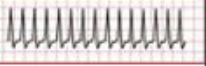


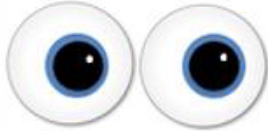









# Comparison of Toxidrome Signs and Symptoms

	HR & BP	Resp.	Temperature	Pupils	Bowel Sounds	Diaphoresis
<p><b>Opioid</b></p> <p>Morphine • Codeine • Tramadol • Heroin • Meperidine • Diphenoxylate • Hydromorphone • Fentanyl • Methadone • Propoxyphene • Pentazocine • DXM • Oxycodone • Hydrocodone</p>						
				<b>Pinpoint</b> 		
<p><b>Sympathomimetic</b></p> <p>Caffeine, cocaine, amphetamines, methamphetamines, Ritalin, LSD, Theophylline, MDMA</p>				<b>Dilated</b> 		
<p><b>Sedative-Hypnotic</b></p> <p>anti-anxiety agents, muscle relaxants, antiepileptics and preanesthetic medications –Barbituates–Benzodiazepines</p>				<b>No change</b> 		

Adapted from Diaz, G. *Toxidromes Compared: Anticholinergic, Cholinergic, Opioid, Sympathomimetic, Sedative-Hypnotic*



# Comparison of Withdrawal Signs and Symptoms

	HR & BP	Resp.	Temperature	Pupils	Bowel Sounds	Diaphoresis
						
<p><del>Sympathomimetic</del> Caffeine, cocaine, amphetamines, methamphetamines, Ritalin, LSD, Theophylline, MDMA</p> <p><b>Opioid Withdrawal</b></p>	 			<p>Dilated</p> 		
<p><del>Sympathomimetic</del> Caffeine, cocaine, amphetamines, methamphetamines, Ritalin, LSD, Theophylline, MDMA</p> <p><b>EtOH Withdrawal</b></p>	 			<p>Dilated</p> 		

Adapted from Diaz, G. *Toxidromes Compared: Anticholinergic, Cholinergic, Opioid, Sympathomimetic, Sedative-Hypnotic*

Adapted from Diaz, G. *Toxidromes Compared: Anticholinergic, Cholinergic, Opioid, Sympathomimetic, Sedative-Hypnotic*. GrepMed [online] Retrieved from <https://www.grepmed.com/images/2593/sympathomimetics-anticholinergics-toxidromes-toxicology-comparison>

# Laboratory and Diagnostics

## Laboratory

- Complete Blood Count
- Complete Metabolic Panel
- Liver Function Tests (LFTs)
- CK
- Lactate
- Troponin

## EKG



# Laboratory and Diagnostics

## Indications for head CT:

- Altered mental status
- Neurologic symptoms
- Signs of physical trauma (eg, TBI)
- Found unconscious or comatose, which can be the result of trauma or stroke, including stimulant-induced stroke
- Anoxic injury

## Indications for lumbar puncture and blood tests for encephalitis

- Unexplained fever
- Meningeal signs and symptoms (eg, stiff neck, photophobia, back pain)

## Indications for EEG:

- Seizure not well explained
- Neurologic signs and symptoms not well explained
- Persistent encephalopathy

ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder

# Management of Stimulant Intoxication

1

Assess for acute issues and complications of stimulant intoxication

2

Monitor vital signs

3

Assess and monitor suicidality

4

Monitor for worsening signs/sx of intoxication and emergent complications

5

Provide adequate hydration

6

Provide a low-stimulation environment

7

Manage the risk of return to stimulant use

8

Coordinate clinical testing as indicated

# Setting Determination

- ◆ Patients with stimulant intoxication are usually managed in acute care settings but some can be managed in lower acuity clinical settings if –
  - ◆ Patient cooperative
  - ◆ Responsive to interventions (e.g., verbal and non-verbal de escalation strategies, medications), that can be managed in setting patient is at.
  - ◆ Mild hyperadrenergic symptoms and responsive to medications (available).
  - ◆ Clinicians able to assess for acute issues and complications, monitor vitals, assess/monitor risk self/other harm (suicidality)
  - ◆ Able to provide hydration
  - ◆ Manage risk to return to use\*
  - ◆ Appropriate clinical testing available or can be coordinated.



## Pharmacologic Management of Stimulant Induced Hyperadrenergic State

### Benzodiazepines

- Benzodiazepines can be considered a first-line treatment for managing stimulant-induced agitation and/or confusion (High certainty, Conditional Recommendation)

### Other GABA agents

- Phenobarbital, propofol

### HTN

- Beta blocker with alpha-1 antagonism (Carvedilol, labetalol)
- Calcium channel blockers
- Nitric oxide mediated vasodilator
  - sodium nitroprusside, phentolamine, or dihydropyridine calcium channel blockers

### Other

- IM ketamine
- Dexmedetomidine, clonidine (Alpha-2 adrenergic agonist)

Richards 2015

# Pharmacologic Management Psychosis

## ◆ Antipsychotics

- ◆ Avoid chlorpromazine and clozapine (seizure threshold)
- ◆ If escalating psychosis or agitation
  - ◆ Conduct medical evaluation to identify life-threatening signs/symptoms that require emergent hospital workup and management.
  - ◆ Conduct mental status exam focused on patient/other safety

# Catecholamine Depletion= “Withdrawal”



DOPAMINE DEPLETION –  
STATE OF EXHAUSTION

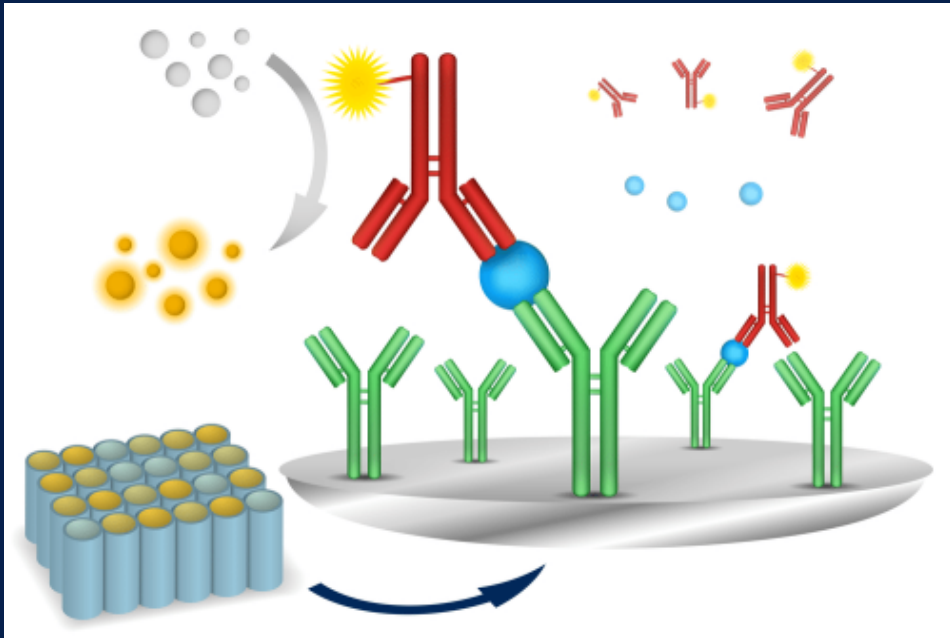


SOME STIMULANTS ALSO  
MAY HAVE SEROTONIN  
DEFICIENCY.

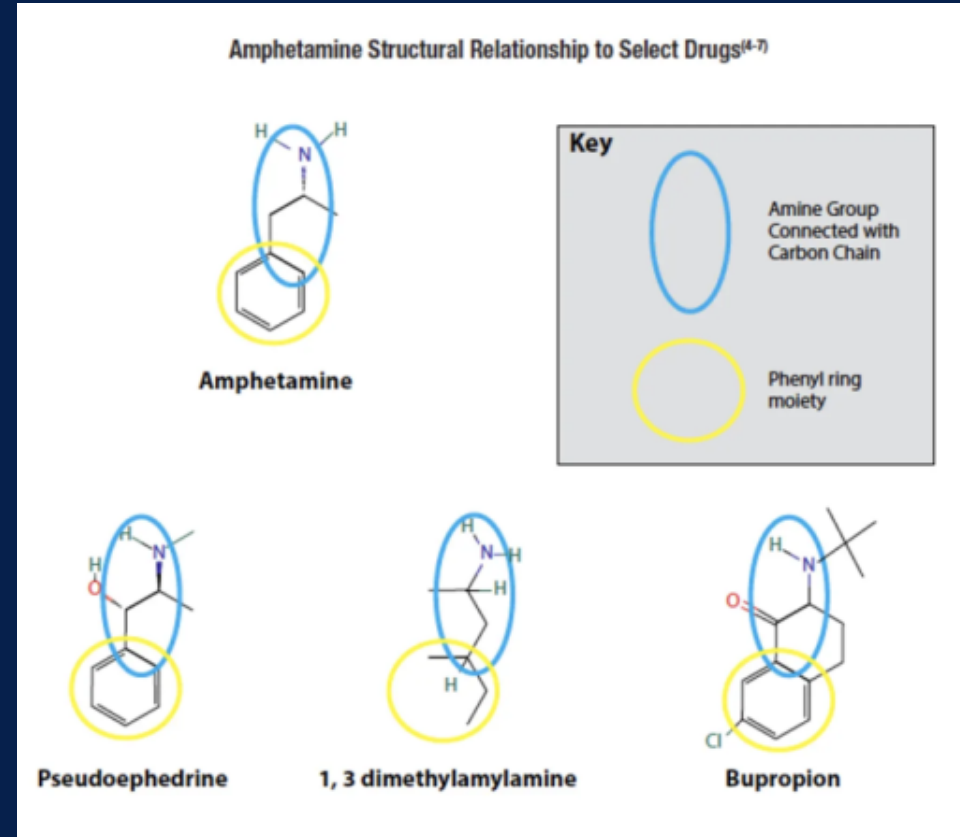


REST, NUTRITION, SLEEP,  
SUPPORTIVE CARE

# Drug Testing: Immunoassay



<https://trinitymedicallaboratories.com/how-does-drug-testing-with-enzyme-immunoassay-work/>

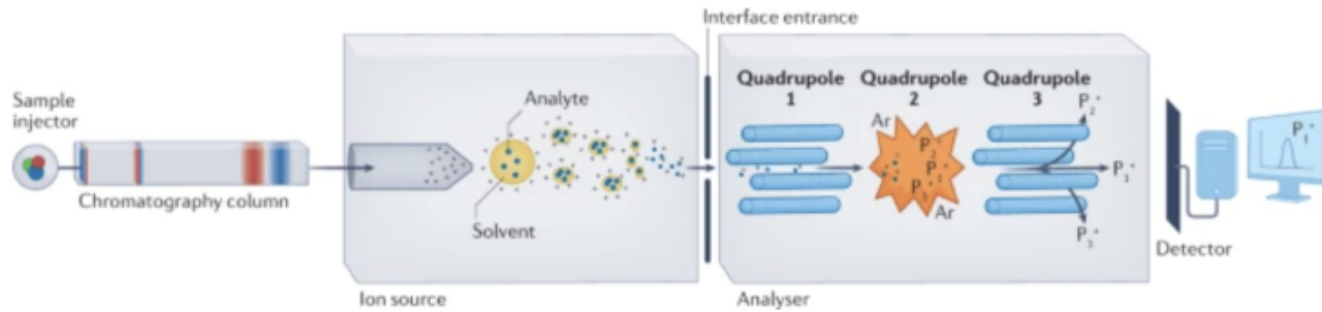


<https://www.medcentral.com/meds/monitoring/false-positive-amphetamine-urine-screens>

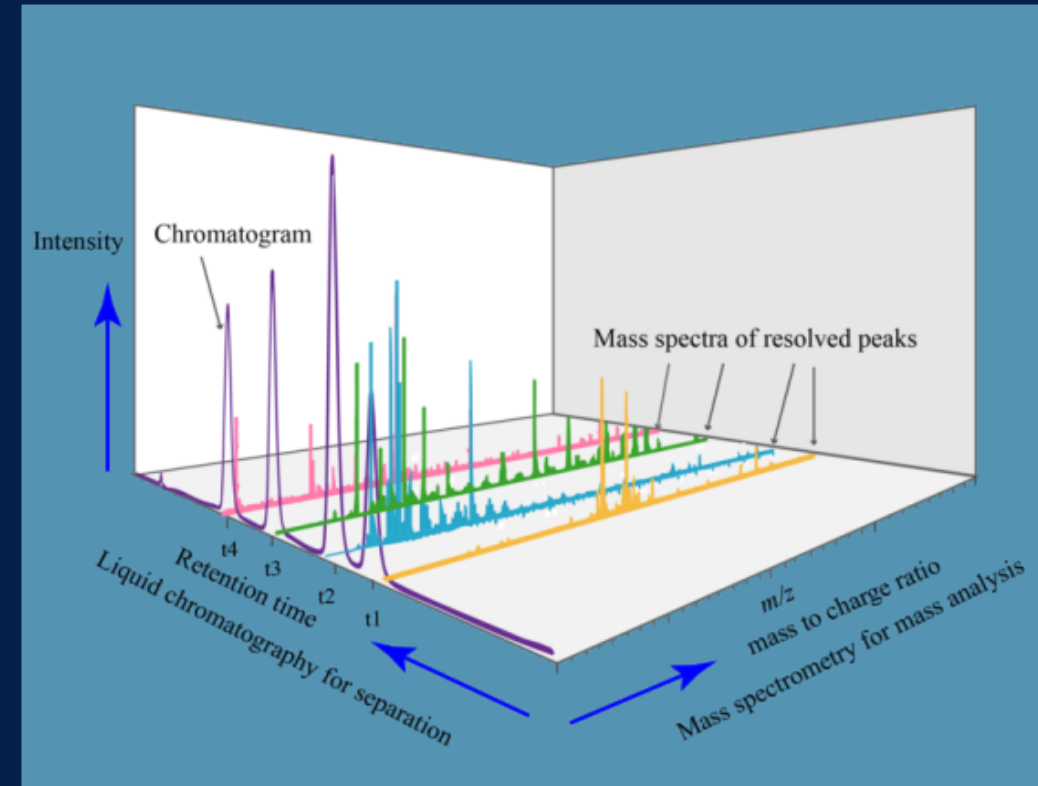


# Liquid Chromatography Mass Spectrometry

**Fig. 1: Depiction of a liquid chromatography–tandem mass spectrometry system.**



Electrospray ionization shown as the ion source with a triple quadrupole analyser.



Left Image: Thomas, S.N., French, D., Jannetto, P.J. et al. 2022

Right Image: [Public Domain](#), credit Daniel Norena-Caro

# False Positives

Drug name	Type of drug test (cut-off concentration)	Dosage <sup>1</sup> Concentration in urine <sup>2</sup>	Ref.
Amantadine	fluorescence polarization immunoassay ADx* — Abbott Laboratories, Abbott Park, Illinois (N.M.)	N.M.	[6]
Aripiprazole	N.M. (UDS immunoassay with 300 µg/L cut-off) N.M. (UDS immunoassay) Beckman Coulter AU680 Analyzer EMIT II Plus, Brea, CA (500 µg/L)	15–45 mg single dose <sup>1</sup> 15–39 mg/day <sup>1</sup> (256–452.5 µg/L) <sup>2</sup> 30 mg/day <sup>1</sup>	[7–9]
Atenolol	Amphetamine assay (300 µg/L)	750,000 µg/L <sup>2</sup>	[10]
Atomoxetine	Amphetamine assay (N.M.)	120 mg — 12 h before test <sup>1</sup>	[11]
Bisoprolol	Amphetamine assay (300 µg/L)	400,000 µg/L <sup>2</sup>	[10]
Bupropion	Amphetamine assay (300 µg/L) Plus immunoassay (N.M.)	8,500 µg/L <sup>2</sup>	[10] [12]
Erythro-dihydro bupropion	Syva EMIT II Plus immunoassay (300 µg/L)	22,000 µg/L <sup>2</sup>	[13]
(±)-Hydroxybupropion	Syva EMIT II Plus immunoassay (300 µg/L)	62,000 µg/L <sup>2</sup>	[13]
Brompheniramine	monoclonal EMIT d.a.u. Amphetamine Immunoassay (Syva Co., Palo Alto, CA) (N.M.)		[14]
Ceftaroline fosamil	Homogeneous enzyme immunoassay Abbott MULTIGENT* (500 µg/L)	53,100 µg/L <sup>2</sup>	[15]
Chlorpromazine	Syva EMIT-MAM Roche Hitachi 911w platform (1000 µg/L)		[5]
Chloroquine	DRI Amphetamine Assay on an Architect C16000 analyzer — Abbott Diagnostics-Santa Clara, CA (For both 1000 µg/L)	155 mg single dose <sup>1</sup> 100,900 µg/L <sup>2</sup>	[16]

Do NOT memorize!!



# False Positives

	and 500 µg/L) Syva Emit II Plus Amphetamines assay (500 µg/L)		
<b>Clobenzorex Hydrochlorate</b>	GC/MS	30 mg oral dose 1–7 h before test	[17]
<b>Doxepin</b>	Fluorescence Polarization Immunoassay Adx* — Abbott Laboratories, Abbott Park, Illinois (N.M.)	N.M.	[18]
<b>Ephedrine</b>	Triage* DOA kit (650 µg/L) Amphetamine UDT Immunoassays (N.M.)	N.M.	[19] [20] [21]
<b>Esmolol</b>	Homogeneous enzyme immunoassay Abbott MULTIGENT* (500 µg/L)	237,300 µg/L <sup>2</sup>	[15] [22] [23]
<b>Esmolol acid</b>	Homogeneous enzyme immunoassay Abbott MULTIGENT* (500 µg/L)	446,400 µg/L <sup>2</sup>	[15]
<b>Famprofazone</b>	CEDIA immunoassay (N.M.)	100 mg — 6 h before test <sup>1</sup>	[24]
<b>Fenfluramine</b>	Amphetamine immunoassay screens (N.M.)		[20]
<b>Fenofibrate</b>	amphetamine/MDMA CEDIA (1000 µg/L)	daily dose of 267 mg <sup>1</sup>	[25] [26]
<b>Imatinib</b>	Immunoassy-based UDT (N.M.) Homogeneous enzyme immunoassay Abbott MULTIGENT* (500 µg/L)	400 mg/d <sup>1</sup> 216,600 µg/L <sup>2</sup>	[27] [15]
<b>Labetalol</b>	Abbott TDx amphetamine/methamphetamine II kit (N.M.) Syva EMIT d.a.u, polyclonal amphetamine class kit (N.M.) Syva EMIT d.a.u, monoclonal amphetamine kit (N.M.)	800 mg tid <sup>1</sup> 800 mg tid <sup>1</sup>	[28] [29]

Stoeva Stanil  
2023

# False Positives

Drug name	Type of drug test (cut-off concentration)	Dosage <sup>1</sup> Concentration in urine <sup>2</sup>	Ref.
Mebeverine	Fluorescence polarization immunoassay (300 µg/L)	single oral dose of 405 mg — 16 h before test <sup>1</sup>	[30]
Metformin	Biosite Triage (N.M.)	N.M.	[5]
Methyldopa	Homogeneous enzyme immunoassay Abbott MULTIGENT* (500 µg/L)	N.M.	[15]
α-Methyldopamine	Homogeneous enzyme immunoassay Abbott MULTIGENT* (500 µg/L)	13,600 µg/L <sup>2</sup>	[15]
Methylphenidate	CEDIA; Microgenics, Pleasanton, CA (1 µM/mL) CEDIA amphetamine assay (300 µg/L)	125,000 µg/L <sup>2</sup>	[31] [10]
Metoprolol	enzyme immunoassay Abbott MULTIGENT* (500 µg/L) CEDIA (300 µg/L)	20,000 µg/L <sup>2</sup> 300,000 µg/L <sup>2</sup>	[32] [10]
Mexiletine	CEDIA (300 µg/L) integra KIMS (500 µg/L) cobas KIMS (500 µg/L) t specimen POC (1000 µg/L) multi 14 + 3 POC (1000 µg/L) AU Syva emit II (500 µg/L) ista Syva emit II (1000 µg/L)	25,000 µg/L <sup>2</sup> 50,000 µg/L <sup>2</sup> 25,000 µg/L <sup>2</sup> 500,000 µg/L <sup>2</sup> 1000,000 µg/L <sup>2</sup> 50,000 µg/L <sup>2</sup> 50,000 µg/L <sup>2</sup>	[10] [33]
Moxifloxacin	Homogeneous enzyme immunoassay Abbott MULTIGENT* (500 µg/L)	350,000 µg/L <sup>2</sup>	[34]
Ofloxacin	TdxFlx AM/MA II (300 µg/L)	N.M.	[5]
Perazine	N.M.	N.M.	[35]

Again....Do NOT  
memorize!!

Stoeva Stanil  
2023

# False Positives

Phendimetrazine	ELISA technique adapted for the detection of amphetamines in hair (N.M.)	N.M.	[36]
Phenethylamine	Amphetamine UDT Immunoassays (N.M.)	N.M.	[21]
Phentermine	EMIT II (300 µg/L) Bio-Quant Direct ELISA (N.M.)	7,500 ng/mL <sup>2</sup>	[10] [21]
Phenylpropanolamine	monoclonal EMIT d.a.u. Amphetamine Immunoassay	N.M.	[14] [22]
Procainamide	Homogeneous	23,200 µg/L <sup>2</sup>	[15]
N-acetyl-3-hydroxyprocainamide	Homogeneous	92,200 µg/L <sup>2</sup>	[15]
Promethazine		N.M.	[5]
Propranolol		41,000 µg/L <sup>2</sup>	[13]
Propylhexedrine	Several	N.M.	[21]
Pseudoephedrine	Several amphetamine UDT Immunoassays (N.M.)	N.M.	[21]
Ranitidine	monoclonal EMIT d.a.u. Amphetamine Immunoassay — Syva Co., Palo Alto, CA (N.M.) CEDIA (300 µg/L) Beckman Coulter Synchron CX5CE (1000 µg/L)	91,000 µg/L <sup>2</sup> 225,000 µg/mL <sup>2</sup> 43,000 µg/L <sup>2</sup>	[22] [10] [37]
Selegiline	N.M. GC/MS	N.M.	[38]

Remember this instead...Do NOT memorize!!

Stoeva Stanil  
2023

Stoeva Stanila\*, 2023

# False Positives

Sertraline	CEDIA (300 µg/L)	200,000 µg/L <sup>2</sup>	[10]
Sildenafil		25,000 µg/L <sup>2</sup>	[10]
Tapentadol		25,000 µg/L <sup>2</sup>	[10]
Tetracaine		40,000 µg/L <sup>2</sup>	[39]
Tolmetin	A	N.M.	[20]
Tramadol		12,500,000 µg/L <sup>2</sup>	[10]
Tranlycypromine		20,000 µg/L <sup>2</sup>	[13]
Trazodone (m-CPP)	Syva Ecstasy EMIT II (N.M.) Amphetamines II (300 µg/L)	3,000 µg/L <sup>2</sup> 6,700 µg/L <sup>2</sup>	[5]

Whew!

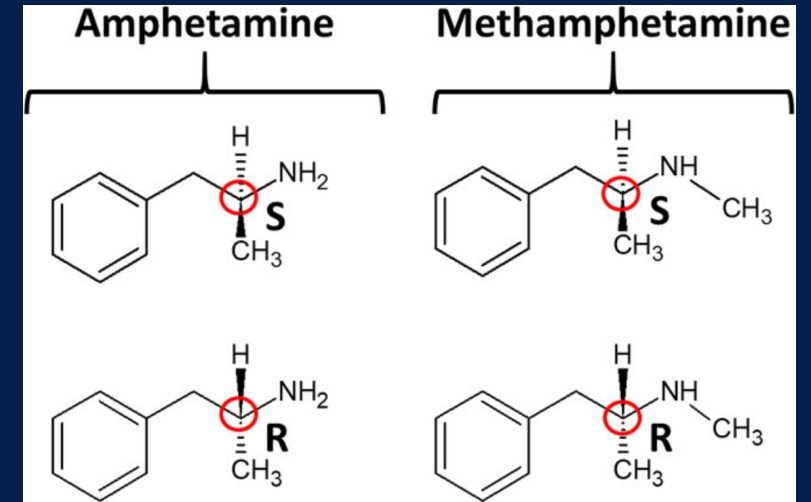
Stoeva Stanil  
2023

Stoeva Stanila\*, 2023



# False Positives - Methamphetamine

- ◆ Methamphetamine is rapidly demethylated to amphetamine
- ◆ Most common result is positive for both
- ◆ Federal workplace testing guidance requires presence of both methamphetamine and amphetamine to report positive
- ◆ Enantiomer testing available, rarely used



# True Positives



**Table 1. OTC and Prescription Drugs Containing or Metabolized to Methamphetamine**

Product (Class)	Indication	Drug	Predominant Isomer
Vicks VapoInhaler (OTC)	Decongestant	Levmetamfetamine	<i>l</i>
Selegiline (Eldepryl) (Rx only)	Parkinsonism	Selegiline	<i>l</i> (as a metabolite)
Didrex (C-III)	Obesity	Benzphetamine	<i>d</i> (as a metabolite)
Desoxyn (C-II)	ADHD, obesity	Methamphetamine	<i>d</i>
Illegally manufactured methamphetamine (ie, "crystal meth") (C-II)	No known medical use	Methamphetamine	>20% <i>d</i>

ADHD, attention deficit hyperactivity disorder; OTC, over the counter  
Based on references 5-8.



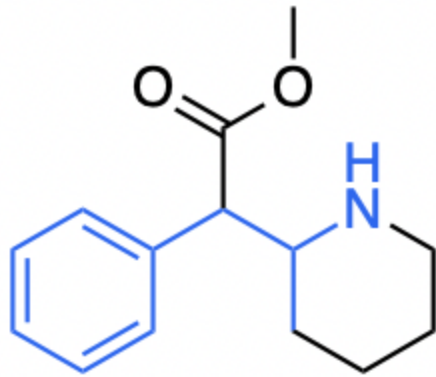
# Drug Testing Caveats

## ◆ Methylphenidate?

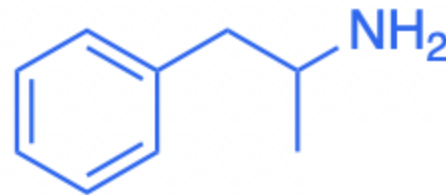
- Methylphenidate has not caused false-positive results (EMIT, Siemens Healthcare Diagnostics) (Breindahl et al. 2012)

## ◆ Fentanyl?

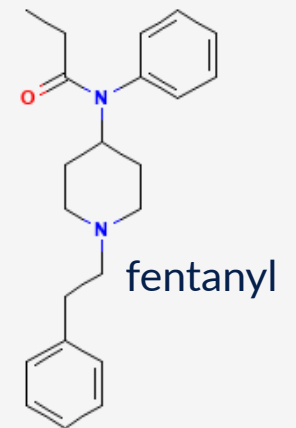
- “The New York State Police Forensic Toxicology Laboratory investigated a trend of false-positive fentanyl urine drug screens and determined that **urine methamphetamine levels greater than 40 µg/mL can cause a false-positive urine fentanyl screening result using the Neogen enzyme-linked immunosorbent**



methylphenidate



amphetamine



fentanyl

# ASAM Appropriate Use of Drug Testing Consensus

- ◆ Informs clinical decision-making
- ◆ Does not diagnose nor rule out SUD
- ◆ Use results in combination with patient history, physical exam, and psychosocial assessment to determine care plan
- ◆ Can be important supplement to patient self-report due to adulterant
- ◆ Individualize test selection based on specific patients and clinical scenarios.
- ◆ Understand benefits and limitations of each test and matrix
- ◆ Definitive testing should be used when the results inform clinical decisions with major clinical or nonclinical implications

# Drug Testing Summary

- ◆ Limited utility depending on goals.
- ◆ Limits of urine testing.
- ◆ Designer/Novel Psychoactive Substance Stimulants –not going to show up on standard screens and if available send out as blood test (delay to results).
- ◆ Often a “designer stimulant panel” limited utility not updated to current landscape of available drugs, \$\$\$, negative doesn’t mean wasn’t exposed to a stimulant.
- ◆ When in doubt, use confirmatory testing and patient history

# Pharmacology for Stimulant Use Disorder

Antidepressants

Mirtazapine

Bupropion

Cognitive  
stimulants

Dexamphetamine

Modafinil

Anti-craving

Naltrexone (with or without bupropion)

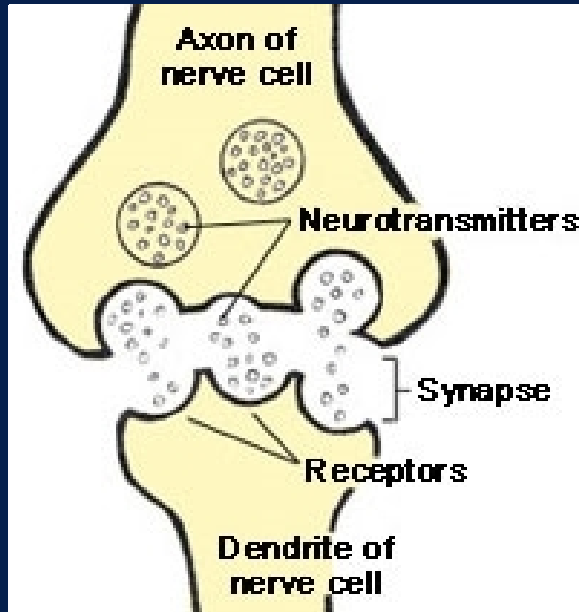
Baclofen

Off Label

Brensiver, M et al 2013



# Bupropion Toxicity



- ◆ Norepinephrine-dopamine reuptake inhibitor
- ◆ Overdose
  - ◆ Seizures
  - ◆ Tachycardia
  - ◆ Agitation
  - ◆ Cardiovascular
    - ◆ Conduction delays
    - ◆ Prolonged QRS/Qt interval → arrhythmia

# CASE

- ◆ 37 year-old M
  - ◆ Hx severe opioid use disorder (OUD) and StUD with smoked fentanyl and methamphetamine
  - ◆ admitted to an inpatient detoxification facility (ASAM level 3.7.
  - ◆ last use of methamphetamine /fentanyl ~1 hour prior to presentation
- ◆ HR 110 bpm, BP 164/96 mmHg, RR 24 breaths/minute, Temp 99.4 F.
  - ◆ Mild sweating, dilated pupils, some psychomotor agitation and anxiety but completes intake process and interacts appropriately with staff.
- ◆ Prior to admission: outside one last time
  - ◆ More anxious , pacing
  - ◆ Interacting loudly with other staff/clients

# CASE

- ◆ The Physician is on the unit and witnesses the interaction. They should do which of the following first?
  - ◆ A.) Immediately order 5 mg oral olanzapine to help calm the patient who appears to have acute stimulant intoxication.
  - ◆ B.) Call for an ambulance to transport the individual to the Emergency Department for a higher level of care and more aggressive options for treatment of his acute intoxication and/or withdrawal.
  - ◆ C.) The clinician should start with verbal and nonverbal de-escalation strategies to calm the patient and attempt to identify causal factors for his agitation and perform a more comprehensive assessment if the patient is cooperative and not in acute distress.
  - ◆ D.) The patient should have a dose of 10 mg diazepam be given PO and then vitals checked in an hour.
  - ◆ E.) None of the above are the correct answer.

# Case

- ◆ After further questioning
  - ◆ When I went out to smoke, swallowed a gram of methamphetamine
- ◆ Pulse 130-140bpm



# Case

The physician asks for an ambulance stat. Which of the following are appropriate given this evolving situation.

A.) If the patient is able to take a dose of diazepam PO (IV or IM not available at this level of care) they should receive asap unless it delays any assessment by EMS/first responders or transport.

B.) If safe to obtain a set of vitals the patient should have vitals including core temperature obtained at this point.

C.) as long as safe to do so the patient should be brought to a quiet area to wait for the ambulance ideally out of the regular milieu of the unit (while the other activities are performed and ambulance is en route).

D.) A provider should continue to calm and de escalate the patient while they wait for the ambulance –as long as it is safe to do so.

E.) All of the above are correct actions in this situation.

# Final Takeaways

- ◆ The stimulant class covers a broad range of substances and pharmaceuticals
- ◆ Stimulant neurotransmission involves serotonin, dopamine, and norepinephrine leading to characteristic effects
- ◆ Benzodiazepines are one of the first line agents for treating hyperadrenergic states from stimulant intoxication

# Reference

1. <https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates>
2. <https://www.asam.org/quality-care/clinical-guidelines/stimulant-use-disorders>
3. Rasmussen N. Amphetamine-Type Stimulants: The Early History of Their Medical and Non-Medical Uses. *Int Rev Neurobiol.* 2015;120:9-25.
4. Richards, J. R., Albertson, T. E., Derlet, R. W., Lange, R. A., Olson, K. R., & Horowitz, B. Z. (2015). Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. *Drug and alcohol dependence*, 150, 1-13.
5. Nelson L.S., & Howland M, & Lewin N.A., & Smith S.W., & Goldfrank L.R., & Hoffman R.S.(Eds.),Eds. Lewis S. Nelson, et al. McGraw-Hill Education, 2019, <https://accessemergencymedicine.mhmedical.com/content.aspx?bookid=2569&sectionid=210256528>.
6. Mahoney III, J. J., Kalechstein, A. D., De La Garza, R., & Newton, T. F. (2008). Presence and persistence of psychotic symptoms in cocaine-versus methamphetamine-dependent participants. *The American journal on addictions*, 17(2), 83-98
7. Stoeva Stanila\*, Common Causes of False Positive and False Negative Results in Amphetamine Screening Tests, *Current Analytical Chemistry* 2023; 19 (8)
8. Broussard, L. (2019). Chapter 16 - Critical Issues When Testing for Amphetamine-Type Stimulants: Pitfalls of Immunoassay Screening and Mass Spectrometric Confirmation for Amphetamines, Methamphetamines, and Designer Amphetamines. In A. Dasgupta (Ed.), *Critical Issues in Alcohol and Drugs of Abuse Testing (Second Edition)* (pp. 207–214). Academic Press. <https://doi.org/10.1016/B978-0-12-815607-0.00016-2>
9. Campbell, J. L., Kafle, A., Bowman, Z., Blanc, J. C. Y. L., Liu, C., & Hopkins, W. S. (2020). Separating chiral isomers of amphetamine and methamphetamine using chemical derivatization and differential mobility spectrometry. *Analytical Science Advances*, 1(4), 233–244. <https://doi.org/10.1002/ansa.202000066>
10. Torben Breindahl, Peter Hindersson, Methylphenidate is Distinguished from Amphetamine in Drug-of-Abuse Testing, *Journal of Analytical Toxicology*, Volume 36, Issue 7, September 2012, Pages 538–539, <https://doi.org/10.1093/jat/bks056>
11. Justin L Abbott, Jennifer F Limoges, Kelly J Virkler, Seth J Tracy, Gregory G Sarris, ELISA Screens for Fentanyl in Urine Are Susceptible to False-Positives in High Concentration Methamphetamine Samples, *Journal of Analytical Toxicology*, Volume 46, Issue 4, May 2022, Pages 457–459, <https://doi.org/10.1093/jat/bkab033>
12. Thomas, S.N., French, D., Jannetto, P.J. et al. Liquid chromatography–tandem mass spectrometry for clinical diagnostics. *Nat Rev Methods Primers* 2, 96 (2022). <https://doi.org/10.1038/s43586-022-00175-x>
13. Abbott DL, Limoges JF, Virkler KJ, Tracy SJ, Sarris GG. ELISA Screens for Fentanyl in Urine Are Susceptible to False-Positives in High Concentration Methamphetamine Samples. *J Anal Toxicol.* 2022 Apr 21;46(4):457-459. doi: 10.1093/jat/bkab033. PMID: 33835171.